

LETTERS TO THE EDITOR

Sustained downgaze in coma after cardiac arrest

Sustained downgaze eye deviation is occasionally associated with lesions affecting the dorsal midbrain, usually thalamic haemorrhage. In stuporous or comatose patients, however, this downgaze does not necessarily indicate structural pretectal damage.¹ Subarachnoid haemorrhage, seizure, hepatic failure, hypoglycaemia, intoxication with sedative drugs, and hypoxic encephalopathy can cause this eye sign in comatose patients.¹ We report on three comatose patients who showed sustained downgaze after cardiac arrest. The paper concentrates particularly on the temporal neuro-ophthalmological profile.

Between January and December 1998 we examined three patients with sustained downgaze. All three patients underwent brain CT and EEG while sustained downgaze was present (table 1). Brain MRI was performed only in patient 2, 2 weeks after admission. All patients were in a comatose state after cardiac arrest, responding only to painful stimuli. Deep tendon reflexes were slightly increased in patient 1 but normal in patients 2 and 3. Flexor plantar reflexes were elicited in all patients. Cardiac arrest was due to anaphylaxis in patient 1, cardiomyositis in patient 2, and ventricular fibrillation in patient 3. Arrest time ranged from 10 to 30 minutes before resuscitation. All patients had not received any sedative drugs.

Sustained downgaze deviation was recognised in each patient when the eyelids were raised after a period of 1 to 4 days, when the immediate post-resuscitation threat of death had subsided. Horizontal oculocephalic responses were present in all patients, and the eyes could be driven upward with vertical oculocephalic manoeuvres. The pupils were normal in size and showed normal reactions to light. In patient 1, high frequency horizontal head shaking was followed by transient conjugate upward ocular deviation. After a few seconds of horizontal head shaking at a frequency of 2 Hz, the eyes moved slowly upwards, remained there for a few seconds, and lowered slowly. This phenomenon was recognised only while sustained downgaze was evident. This upward ocular deviation could not be elicited in the other two patients. In patient 2, smooth and then saccadic ping-pong gaze² was detected transiently 2 days after admission; the ping-pong gaze disappeared when the eyes began to deviate downward 4 days after admission. Marked rigidity

and dorsiflexion of the neck and trunk were associated with sustained downgaze in this patient; rigidity of the limbs was mild. This abnormal rigidity and dorsiflexion resolved with the disappearance of the sustained downgaze. Muscle tone of the other two patients was slightly decreased.

Brain CT findings in all patients and MRI findings in patient 2 seemed normal. An EEG showed a generalised delta rhythm intermingled with theta waves in patient 1, low voltage fast activity in patient 2, and suppression burst in patient 3. The sustained downgaze disappeared within 1 week in all patients, but all have remained in a persistent vegetative state.

Our three patients experienced acute onset coma as a result of diffuse CNS damage after cardiac arrest. The EEG results in our patients suggested the existence of diffuse, severe brain damage. The ping-pong gaze seen in patient 2 also implied severe bilateral cerebral damage.² The sustained downgaze appeared in our patients 1 to 4 days after resuscitation. That was also the time at which patients were emerging from the most critical postevent stage. In a previously reported patient with hypoxic encephalopathy, downgaze was recognised after 2 weeks of coma.¹ These findings suggest that sustained downgaze is not an eye sign in dying patients but that it appears in patients reaching an early recuperation stage. This notion is supported by our finding that the ping-pong gaze changed from a smooth to a saccadic pattern before appearance of the sustained downgaze in one patient; such transition suggests clinical improvement.² It remained unclear which function might have improved as a prerequisite for the sustained downgaze.

Keane reported sustained upgaze deviation after cardiac arrest.³ Our present findings indicate that sustained downgaze may also be associated with hypoxic encephalopathy after cardiac arrest. The most striking difference between the sustained upgaze reported by Keane³ and sustained downgaze is the time of appearance; sustained upgaze appears immediately after cardiac arrest whereas sustained downgaze is recognised after a few days. The temporal relation between the upgaze or downgaze and ping-pong gaze² confirms this difference as ping-pong gaze is reported to appear after resolution of sustained upgaze,³ whereas it preceded sustained downgaze in our patient. Keane speculated that the sustained upgaze deviation after cardiac arrest resulted from hypoxic cerebellar damage due to diffuse CNS hypoperfusion.³ The possible mechanism of upgaze deviation with cerebellar damage is a disinhibition of anterior canal projections for upward vestibulo-ocular reflex caused by bilateral floccular dysfunction.⁴ When this has recovered, the subsiding depression of mesencephalic neuronal circuits for upgaze might explain subsequent downgaze deviation. Sustained upgaze may be a direct result of diffuse

CNS hypoperfusion in which the cerebellum is severely impaired,³ and sustained downgaze may be a result of partial recovery from diffuse, severe cerebral depression. This is consistent with the fact that all our patients with sustained downgaze lived, although they remained in a persistent vegetative state, whereas almost all reported patients with sustained upgaze died.³

One of our patients showed transient upward eye deviation after high frequency horizontal head shaking during the period of sustained downgaze. Walker and Zee⁵ described high frequency horizontal head shaking as transiently leading to and increasing upward slow eye movements that result in downbeat nystagmus in patients with cerebellar degeneration. Thus, the upward eye deviation after horizontal head shaking in our patient may imply severe underlying cerebellar damage.

Our second patient had marked rigidity and dorsiflexion of the neck and trunk during the period of sustained downgaze. Rigidity and dorsiflexion are typical symptoms of progressive supranuclear palsy, in which the midbrain tegmentum is severely damaged.⁶ Bilateral lesions of the interstitial nucleus of Cajal, which lies in the midbrain tegmentum, have been reported to result in dorsiflexion of the neck similar to that seen in progressive supranuclear palsy.⁶ It could be that dorsal midbrain involvement was responsible for our patient's rigidity and dorsiflexion.

More than one anatomical site or physiological mechanism may well be involved in forced downgaze in comatose patients after cardiac arrest, and the mechanistic details of this state are still unclear. However, it is important to recognise that sustained downgaze can appear transiently a few days after cardiac arrest and resuscitation.

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Table 1 Clinical data of the patients

Patient No./age/sex	Cause of cardiac arrest	Arrest time (min)	Sustained downgaze			EEG findings	Outcome
			Latent period (days)	Duration (days)	Associated sign(s)		
1/68/F	Anaphylaxis	10	2	5	Transient upward eye deviation after head shaking	Delta-theta waves	Vegetative
2/22/M	Cardiomyositis	15	4	2	Rigidity and dorsiflexion of the neck	Low voltage fast activity	Vegetative
3/70/M	Ventricular fibrillation	30	1	3	—	Suppression burst	Vegetative

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Prion protein gene polymorphism and Alzheimer's disease: one modulatory trait of cognitive decline?

Although its main biological function is still unknown, the prion protein is involved in normal synaptic function.¹ Interestingly, the presence of a valine (V), replacing a methionine (M) at codon 129 of the prion protein gene (PRNP), has been associated with poor performance in cognitive tests in a large cohort of aged, non-demented, French people.² Accordingly, this polymorphic gene represents a suitable candidate for an association with Alzheimer's disease, a dementing disorder characterised by neuronal degeneration and synaptic loss. To assess whether the PRNP V/M codon129 polymorphism—alone or in combination with polymorphisms in the apolipoprotein (APO)E³ and interleukin (IL)-1 α ⁴ genes, already shown to be associated with Alzheimer's disease—affects the occurrence or clinical features of the disease, we performed a case-control study in a cohort of Italian patients with sporadic Alzheimer's disease and age matched healthy controls.

Venous blood was collected from 212 Italian patients (130 women, 82 men; mean (SD) age at disease onset 68.3 (8.0) years) affected by clinically probable Alzheimer's disease, according to McKhann's criteria. Patients were also divided into those with early disease onset (≤ 65 years; 72 patients; mean (SD) age at disease onset 57.0 (7.5) years), and those with a late onset (> 65 years; 140 patients; mean (SD) age at disease onset 73.1 (5.4) years). Blood was also collected from 201 age and ethnicity matched healthy controls (80 women, 121 men; mean (SD) age 67.2 (10.5) years), chosen among the participants in the Italian Longitudinal Study on Aging who were not affected by neurological diseases. At the time of blood collection, we recorded in all subjects a mini mental state examination (MMSE) score (score for inclusion as control subject $> 24/30$) and—only in patients with Alzheimer's disease—the duration of the disease.

The PRNP codon 129 M/V polymorphism was analysed by polymerase chain reaction followed by BsaA1 restriction endonuclease digestion, as previously described.² To overcome the paucity of VV homozygous subjects (6% in patients with Alzheimer's disease and 10% in healthy controls, table 1), all analyses,

except verification of the Hardy-Weinberg equilibrium, were focused on the combination of MV and VV (V+) compared with MM genotypes. APOE $\epsilon 2-4$ and IL-1 α -889 T to C polymorphisms were determined as described.^{3,4} Allele frequency and genotype frequency of PRNP, APOE, and IL-1 α polymorphisms were compared by χ^2 test in case-control (Alzheimer's disease *v* healthy controls) and case-case (early onset Alzheimer's disease *v* late onset Alzheimer's disease) analyses. The relative risk for Alzheimer's disease conferred by the carriage of PRNP V+ or MM genotypes was estimated by Cochran-Mantel-Haenszel odds ratios (ORs). Age, sex, APOE, and IL-1 α adjusted ORs were computed by logistic regression. MMSE scores recorded in V+ and in MM carriers were compared by non-parametric rank sum test and their association with disease duration was assessed by the Spearman correlation coefficient.

The PRNP allele and genotype frequency did not differ significantly between patients with Alzheimer's disease and controls (allele frequency: $p=0.06$; 3×2 genotype frequency: $p=0.12$). The V allele conferred a non-significant OR for Alzheimer's disease of 0.71 (95% confidence interval (95% CI) 0.48–1.06; $p=0.09$; p for trend of the V allele in Alzheimer's disease=0.04). Moreover, PRNP allele and genotype frequency were not affected by sex ($p=0.18$ in Alzheimer's disease and 0.28 in controls), APOE $\epsilon 4$, or IL-1 α TT carrier status (data not shown). Stratification of the Alzheimer's disease cohort by age at disease onset showed that, although not significantly, V+ genotype carriers were more represented among patients with early onset (47%) than those with late onset disease (37%), resulting in an OR for early onset disease due to the carriage of the V+ genotypes of 1.46 (95% CI 0.85–2.69, $p=0.2$). However, a Kaplan-Meier analysis failed to confirm this differential distribution among patients with Alzheimer's disease, indicating that if an association existed, it was small. When we compared patients with early onset and patients with late onset disease with their respective age matched controls, we found that the V+ genotypes were associated with an OR for Alzheimer's disease of 0.92 (95% CI 0.48–1.74; $p=0.8$) in the younger age group (≤ 65 years), and of 0.63 (95% CI 0.38–1.04; $p=0.07$) in the older age group (> 65 years; allele frequency: $p=0.03$, genotype frequency: $p=0.04$, table 1).

As expected, MMSE scores showed a negative correlation with duration of Alzheimer's disease ($r=-0.38$, $p=0.0001$), but not with PRNP genotypes ($p=0.08$). Interestingly, despite a comparable education level (mean number of years in school: V+=7.41; MM=7.52) and a similar median MMSE score recorded at the time of blood collection (15.1 in V+ and 15.3 in MM), V+ carriers had a median disease duration 9 months shorter than MM carriers (38 *v* 47 months; $p=0.038$), possibly indicating a faster deterioration rate in V+ patients.

In conclusion, we failed to detect a significant association between the PRNP codon 129 polymorphism and the occurrence of sporadic Alzheimer's disease in Italy, irrespective of APOE and IL-1 α genotype status, age, or sex. Combarros *et al* recently reported similar results in another southern European population of comparable size.⁵ However, our results suggest that patients with Alzheimer's disease carrying at least one V allele might have an earlier onset of the disease and a small but significant acceleration in their cognitive decline when compared with MM carriers. This is not a surprise as, in multigenic diseases, selected characteristics of the natural history of the disease seem more prone to be influenced by gene polymorphisms than mere occurrence of disease.

In conclusion, two independent studies have now provided evidence against PRNP as a susceptibility gene for sporadic Alzheimer's disease. Our study, however, suggests a possible modulation of disease activity due to the PRNP codon 129 polymorphism. A longitudinal assessment of a large cohort of patients with Alzheimer's using a full battery of cognitive tests might be necessary to confirm our finding.

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Table 1 PRNP 129 genotype and allele frequency in patients with Alzheimer's disease (AD) and healthy controls (HC)

	<i>n</i>	<i>Sex</i>		<i>PRNP 129 genotypes (%)</i>			<i>PRNP 129 allele frequency</i>	
		<i>F</i>	<i>M</i>	<i>MM</i>	<i>MV</i>	<i>VV</i>	<i>M</i>	<i>V</i>
Total sample:								
AD	212	130	82	126 (59)	73(35)	13 (6)	0.77	0.23
HC	201	80	121	103 (51)	78(39)	20 (10)	0.71	0.29
Subjects <65 y:								
AD	72	45	24	38 (53)	29(40)	5 (7)	0.73	0.27
HC	91	29	62	48 (53)	35(38)	8 (9)	0.72	0.28
Subjects ≥65 y:								
AD	140	85	55	89 (63)	44(31)*	8 (6)*	0.79	0.21†
HC	110	51	59	55 (50)	43(39)*	12 (11)*	0.70	0.30†

* $p=0.044$, PRNP 129 V+ *v* MM genotype frequency in AD ≥ 65 years compared with age matched HC.

† $p=0.03$, PRNP 129 V/M allele frequency in AD ≥ 65 years compared with age matched HC.

PRNP=Prion protein gene; HC=healthy controls; F=females; M=males; AF=allele frequency; GF=genotype frequency; AD=Alzheimer's disease.

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Complex musical hallucinosis in a professional musician with a left subcortical haemorrhage

Auditory hallucinosis consists of abnormal acoustic perceptions that occur in the absence of a corresponding acoustic stimulus while the patient is aware of their non-real nature.¹

Musical hallucinosis represents a particular type of acoustic hallucinosis, in which the acoustic perception is formed by music, sounds, or songs. It is frequent in psychiatric diseases and is sometimes reported in sensory neural deafness, but rarely after stroke.^{1,2} We describe a case of musical hallucinosis in a professional musician with a left subcortical haemorrhagic lesion, presumably caused by a cavernous angioma.

A 35 year old, right handed man was referred to our inpatient department in July 1999 7 days after the onset of a slight clumsiness of his right hand followed by complex acoustic perceptions. The patient had attended a symphonic concert where an orchestral transcription of Wagner's "Siegfried" was played: the patient is a connoisseur of music and a composer. When he returned home, about 1 hour later, his musical hallucinosis started. Auditory perceptions were described by the patient as a symphonic piece of music performed by an orchestra with numerous kettledrums and percussion instruments. It was a rather familiar music, unknown to him, but similar to what he had heard during the concert. The theme was played in a minor tonality with frequent use of drums and other percussion instruments interspersed with string instruments. A chorus played by string instruments accompanied the theme. The patient said that the music resembled a piece by the late German romantic authors (for example, Mahler, Bruckner, and Wagner's latest works). The music was initially low in intensity but progressively increased; it was perceived in the middle of his head as if he was listening with headphones on. Conflicting emotions occurred: he felt that it was the most frightening and terrifying music he had ever heard and strongly desired to push it out of his mind but, on the other hand, he was deeply fascinated and said that he would like to compose such an exciting piece.

The patient said that during his musical hallucinosis he was able to speak, watch, and understand television programs and to go about his normal activities. He reported that during the phenomenon his hearing was normal and he could hear everything going on around him, such as the noise outside the house (for example, from the road) and all the usual noise going on in his own house.

The musical hallucinosis lasted about 90 minutes and afterwards the patient fell asleep; he did not have musical hallucinosis during the next day on awakening and it did not recur during the next 20 months.

Seven days after the episode the patient was admitted to our department. On admission a neurological examination evidenced

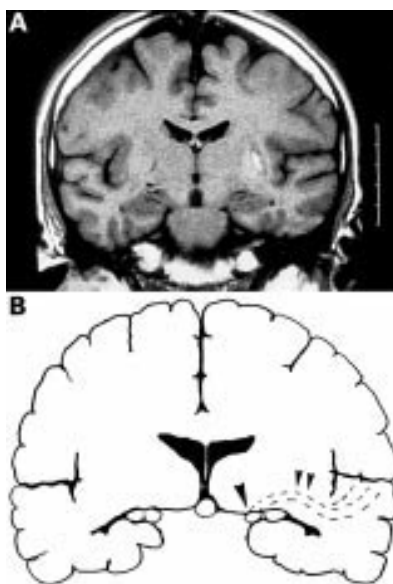


Figure 1 (A) T1 weighted brain MRI and (B) anatomical drawing of the coronal MRI images. An area of altered signal (hyperintense in centre and hypointense at periphery), consistent with a haemorrhagic lesion, involves the left putamen and the external capsule and just touches the acoustic radiation. Comparison between the images outlines the strict relation between the haemorrhagic lesion and the acoustic radiation (double arrows) that runs from the medial geniculate body (single arrow) to the acoustic cortex in the superior temporal gyrus.

only a slight motor impairment of the right hand. His hearing sensation was normal on clinical and instrumental examination. No signs of drug or alcohol misuse were evident. Moreover there was no history of psychiatric disorders.

A cranial CT showed a small hyperdense lesion on the left temporal lobe at subcortical level. Brain MRI (fig 1A) evidenced a haemorrhagic lesion involving the left putamen and the external capsule near the insula. The lesion was located next to the acoustic radiation (fig 1A and B). Cerebral angiography was normal. Three EEG recordings (performed on days 1, 3, and 5 after admission) highlighted only a mild abnormal slow activity at the temporal level, without epileptiform grapho-elements. Audiograms and brain stem auditory evoked potentials were normal.

Transient musical hallucinosis has been described in several situations, such as psychiatric disorders, alcoholism, drug and chemical intoxication, ear and acoustic nerve diseases and, rarely, brain stem lesions mainly involving the tegmentum.^{1,2} Even if musical hallucinosis has been reported in hemispheric lesions² a clear relation with the central acoustic pathway has never been described.

In our patient the prolonged duration of the episode, the preservation of consciousness and memory, and the absence of epileptiform abnormalities on EEG rule out an epileptic genesis of musical hallucinosis. In patients with sensory-neural deafness musical hallucinosis may be determined by an increased cortical excitability due to a deafferentation phenomena¹ or by a spontaneous activation of cerebral areas involved in musical perception.³

In the present case, it might be directly related to the impairment of the acoustic radiation, containing both ascending (excitatory) and descending (inhibitory) fibres. The

inhibitory fibres run from the auditory cortex to lower structures of the central acoustic pathway (medial geniculate nucleus and inferior colliculus) and presumably modulate acoustic perception. The comparison of brain MRI (fig 1A) and of a corresponding anatomical drawing (fig 1B) suggests that the lesion just touches the acoustic radiation between the left medial geniculate body and the auditory cortex. Another explanation of such peculiar findings in our patient may derive from a recent hypothesis regarding musical hallucinosis in acquired deafness: the subcortical lesion may have caused either a disconnection between the primary auditory and the association cortices or an impairment of the "neural networks for the perceptions and imagery of sounds, including the auditory association and the frontal cortex".³ Indeed, the closeness of the lesion to the superior temporal gyrus may interfere with the associative fibres connecting the auditory cortex to the other cerebral areas involved in musical perceptions.

Compared with previously reported cases,¹⁻³ our patient presents several peculiarities. Firstly, the duration of the musical hallucinosis was shorter and the auditory perceptions were heard bilaterally and not lateralised in the opposite ear. Secondly, it occurred in the absence of sensory-neural deafness and might be related to a lesion involving the central acoustic pathway, even at a hemispheric level. This is not in agreement with the notion that complex acoustic hallucinosis is invariably related to damage to the peripheral acoustic pathway or to combined central and peripheral dysfunction.^{1,2} Thirdly, our report greatly supports the role of the dominant hemisphere in musical processing, by contrast with the accepted notion that musical perception is a specific function of the non-dominant hemisphere.^{1,4} We can speculate that the musical training of the patient might have determined the shift of musical representation from the non-dominant to the dominant hemisphere.⁵

Finally, several features of musical hallucinosis in our patient are fascinating. The similarity between the acoustic perceptions and the symphonic music that he had previously heard leads to the hypothesis of an involvement of acoustic memory circuits. The professional experience and the personal sensibility towards symphonic music might both have contributed in the determination of musical hallucinosis influencing the processing of musical sensations.

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Cochlear implantation in a profoundly deaf patient with MELAS syndrome

Cochlear implantation is now an established technology for restoring hearing in profoundly deaf patients. Adults who have lost all useful hearing in both ears are suitable for cochlear implantation if they are profoundly deaf (generally this implies hearing thresholds of 100 dB nHL or worse, across the frequency range 125 to 8000 Hz), with aided hearing thresholds worse than 60 dBA for the frequencies 250 to 4000 Hz and scoring less than 30% in a test of sentence discrimination, using their hearing aids and without lip reading. We describe a patient with MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) who became profoundly deaf and who has successfully undergone cochlear implantation and rehabilitation.

A right handed secretary with MELAS syndrome, and a confirmed A to G mutation at nucleotide 3243 in the mitochondrial genome, was referred to the cochlear implant programme of The Royal National Throat, Nose, and Ear Hospital. She had insulin dependent diabetes, congenital cataracts, short stature, leg weakness, fatigue, and hearing loss. She had never had encephalopathy or strokes. Her mother is also diabetic, has glaucoma, and has a lesser degree of deafness, and her sister has been profoundly deaf from adolescence in addition to having severe mental retardation. The patient had begun to experience bilateral hearing loss at the age of 22, with slow deterioration up to the age of 29, by which time she was profoundly deaf in the right ear. By the age of 30 she was also profoundly deaf in the left ear and had developed tinnitus. She had no spontaneous vertigo, but sudden movements could leave her temporarily unsteady. At the age of 31 she was referred for assessment for cochlear implantation. Her ability to communicate with her family was severely restricted because of her deafness. She had developed a modest lip reading ability and was able to lip read her husband to a limited extent, but relied greatly on finger spelling and written information. Her own voice quality had begun to deteriorate. She was found to have no measurable hearing thresholds except for a 250 Hz tone at 105 dB nHL in the right ear. No tests of speech discrimination were possible, as she had virtually no hearing in either ear. Middle ear impedance was normal, and she had normal bilateral vestibular function on caloric testing. Auditory brain stem responses and electrocochleography showed no peaks in response to wide band clicks presented to either ear at 100 dB nHL, consistent with profound sensorineural deafness. Electrical stimulation of the cochlea, using sinusoidal stimuli presented through a transtympanic needle electrode placed through the tympanic membrane onto the promontory of the middle ear,^{1 2} gave rise to a subjective sensation of hearing in both ears, with better performance on gap detection and temporal difference limen tests on the right. A CT scan of the temporal bones was normal.

The findings listed above showed her to be within the criteria for cochlear implantation, and she was implanted in the right ear at the age of 32 with a Nucleus 22 multichannel

implant. All 22 electrodes were inserted into the cochlea and there were no surgical complications.

Subsequent switch on and rehabilitation went well, and the patient has made good progress. She is able to discriminate environmental sounds well, including different bird-songs, and participate in conversation. Verbal communication with her family has improved. There have been no specific problems with the implant and she is able to converse on the telephone using the implant. The patient has resumed full time work in an office. The tinnitus has remained stable, and there have been no vestibular problems. At the 2 year assessment she scored 97% correct on CUNY/UCL sentences (a British adaptation of a sentence discrimination test developed at City University, New York), using her implant and lip reading and 92% correct on BKB (Bamford, Kowal and Bench) sentences (another speech discrimination test) using her implant but without lip reading. Speech production was within normal limits, although the narrow pitch range reflected her slightly flat pattern of intonation.

MELAS syndrome was first described in 1984 and is one of a group of mitochondrial cytopathies, associated with point genetic mutations. In the brain the characteristic abnormalities are basal ganglia calcification and focal lesions of cerebellar and cerebral atrophy, resulting from cellular rather than vascular dysfunction.³ Although it does not feature in the acronym, hearing loss is a common finding in MELAS. Reports of large kindreds and patient series have shown that at least 50% of patients have a moderate or severe sensorineural hearing loss: 21 of 28 patients with MELAS in an Australian series were deaf,⁴ as were eight of 14 patients in a British series.⁵ The phenotypic expression of the mutation is subject to at least three constraints; the percentage of mutant mitochondrial DNA in the target tissue (which has at most a loose correlation with clinical lesions),⁶ the oxidative stress to which different organs or cell populations are exposed, and as yet unidentified collaborating somatic mutations which enhance selective aspects of the syndrome.

The cochlea is an organ exquisitely vulnerable to oxidative stress. The outer hair cells have a precarious, indirect metabolic support from Deiter cells, and the stria vascularis is both metabolically very active and non-mitotic, hence further subject to mutation accumulation. Recently detailed audiological findings have been reported in 18 patients with MELAS, and the authors argued that the hearing loss in their patients was entirely due to cochlear lesions.⁴ There were excellent speech discrimination scores in six of 12 patients with mild to moderate deafness, and excluding severe and profoundly deaf patients with absent responses, there were normal and symmetric brain stem evoked responses in 18 of 20 latencies recorded from 10 patients. Promontory stimulation testing in two patients was normal, and CT and MRI were reported as showing no lesions which could contribute to hearing loss.

Central auditory lesions have been reported as a cause of hearing loss in MELAS. Imaging studies using both CT and MRI have shown that the occipital and parietal lobes and cerebellum are the brain regions most likely to show focal lesions,³ and a perfusion study using ¹²³I-IMP SPECT, and acetazolamide challenge, showed that patients with MELAS typically have hypoperfusion of the occipital and parietal lobes, with

a significant defect in perfusion reserve.⁶ A case report of a patient who died after having had severe seizures and stroke-like events, and who had had multiple imaging studies, showed mild temporal lobe atrophy at necropsy with associated spongy degeneration of the cortex.⁷ All cortical regions were demonstrated radiologically and pathologically to be abnormal in this patient, with the occipital lobe showing the most marked hypoperfusion. She had become deaf 2 years before her marked clinical deterioration.

The patient we report has had no seizures or stroke-like episodes. Her presenting complaint was hearing loss, which progressed over 8 years to profound deafness. Her selection as a candidate for cochlear implantation was straightforward, and she has been successful in adapting to the device and has gained a significant benefit from it. The performance of the patient in the BKB word tests places her in the top 5% of adult performers in our patient series. Another patient with profound deafness and MELAS, who had had seizures and strokes, has recently been reported incidentally in a large series to have been implanted with a successful outcome, but unfortunately details were not provided.⁴

The fact that this patient has gained considerable benefit from her cochlear implant raises the possibility that other patients with MELAS syndrome and profound sensorineural deafness could benefit from this procedure.

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CORRESPONDENCE

Lead poisoning from complementary and alternative medicine in multiple sclerosis

In response to the article *Lead poisoning from complementary and alternative medicine in multiple sclerosis*,¹ we are very concerned that this

case has been blamed on homeopathic plumbum metallicum that the patient used in an attempt to improve the symptoms of multiple sclerosis. The original article states that he had used a homemade remedy; this is very unlikely to have been prepared using the strict regime applied by homeopathic laboratories. A correctly prepared remedy would only contain minute traces of lead, not enough to cause toxicity.

Certainly a likely explanation (acknowledged in the original article) would have been the lead contained in the pipe he had been using to smoke marijuana.

We consider it worrying when doctors who purport to use modern science to find answers to often difficult questions will, when it suits, simply make assumptions without appropriate testing of the hypothesis in question.

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Anti-GQ1b IgG antibody syndrome without ophthalmoplegia: clinical and immunological features

I read with interest the review by Odaka *et al*¹ of the range of clinical disorders manifesting in patients with raised anti-GQ1b IgG antibodies. Their patients were classified into Miller Fisher syndrome, Bickerstaff's brain stem encephalitis, acute ophthalmoparesis without ataxia, Guillain-Barré syndrome, and "unclassified". The last group included patients who all had external ophthalmoplegia and normal tendon reflexes, and also varying degrees of limb, facial, and bulbar weakness. I have recently encountered a patient who developed an acute, sensory polyneuropathy in association with raised anti-GQ1b IgG antibodies, whose clinical features differ from the 194 patients described in their series.

A previously well 35 year old man had an episode of sore throat and dry cough, with associated myalgia and fever, in May 2000. Two weeks later, he developed tingling paraesthesia first in his feet, spreading up to his knees, and then in both hands. He found it difficult to distinguish where the ground was beneath his feet because of reduced sensation. One week into this illness, he developed partial drooping of his right eyelid. He had no symptoms of weakness or double vision. On examination 3 days later, he had a partial right ptosis, but eye movements were normal and he did not report diplopia. Muscle power and tendon reflexes were normal in all four limbs. He had a rather deliberate gait because of very mild sensory ataxia with reduced sensation to pain, light touch, and vibration sensation in both legs, to the level of the knees. Joint position sense was impaired in the toes but normal in the fingers.

Nerve conduction studies 3 weeks into his neurological illness showed normal distal motor latencies, proximal conduction velocities, and F wave latencies in all four limbs. All sensory nerve action potentials were absent. Protein in CSF was raised at 0.7 g/l (acellular sample). Coxsackie B IgG antibodies were raised at 1:64. Antiganglioside antibody

assays showed raised IgG titres to GQ1b (1:8000), GD1b (1:11000), and GT1b (1:2200). Over the course of the next 2 weeks he improved without treatment, achieving full recovery with no residual symptoms or signs.

The lack of external ophthalmoplegia and ataxia was only encountered in patients classified as Guillain-Barré syndrome in the series by Odaka *et al*,¹ all of whom had limb weakness and reduced or absent reflexes. The electrophysiological findings in this patient were not compatible with criteria for demyelinating or axonal Guillain-Barré syndrome, but repeated studies can rarely be normal.² Electrophysiological studies on patients with Guillain-Barré syndrome with ophthalmoplegia and positive anti-GQ1b antibody titres have shown marked attenuation or absence of sensory nerve action potentials, suggesting that anti-GQ1b antibodies may be particularly involved in sensory nerve conduction failure.³

A recent report of eight cases of sensory Guillain-Barré syndrome has highlighted the existence of this variant.⁴ Two of these patients had normal motor nerve conduction studies, one of whom had essentially normal tendon reflexes. Not all of these patients were tested for antiganglioside antibodies.

The GQ1b ganglioside is present in both sensory and motor nerves, including oculomotor nerves,⁵ and the range of disease associated with anti-GQ1b antibodies could theoretically involve dysfunction in any one or more of these types of nerves in varying degrees. If the screening of antiganglioside antibodies is extended to all patients with Guillain-Barré syndrome and its variants (with or without ocular signs) in a large series, then the clinical range associated with anti-GQ1b antibodies will no doubt expand to include more patients without marked ataxia or external ophthalmoplegia, as in this case.

I thank Dr Hugh Willison, Southern General Hospital, Glasgow, for performing antiganglioside antibody assays, and for helpful comments.

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Odaka and Yuki reply:

Maddison considered that clinical features of his patient were similar to those of "sensory Guillain-Barré syndrome", as proposed by Oh *et al*.¹ All of the patients of Oh *et al* had electrophysiological evidence of demyelination in at least two sensory nerves. By contrast, no evidence of demyelination in sensory nerves was shown in his patient. To produce the evidence, Maddison should have

repeatedly performed sensory nerve conduction studies during the convalescent phase. Because sensory nerve action potentials were absent in his patient, the "syndrome of acute sensory neuropathy" as proposed by Windbank *et al*⁶ may be the diagnosis.

We earlier reported on a patient with a relapsing form of the acute sensory neuropathy syndrome.³ The patient rapidly developed marked sensory ataxia without ophthalmoplegia and limb weakness after an upper respiratory tract infection. The symptoms reached their maximum in a few days, followed by subsequent improvement over a few weeks. However, unsteady gait remained as a chronic deficit. Stepwise progression of his symptoms occurred over 15 years with 10 similar relapses. Sensory nerve conduction studies showed the absence of action potentials, and sural nerve biopsy showed the marked loss of large myelinated fibres. The patient's serum had an extremely high titre of an IgM monoclonal antibody directed against b series gangliosides GD2, GD1b, GT1b, and GQ1b. His IgM reacted neither with GD3 nor with GT1a. An absorption study showed that the anti-GQ1b IgM antibody cross reacted with GD2, GD1b, and GT1b.⁴ The common sugar structure (NeuAc- α 2-8-NeuAc α 2-3 (GalNAc β 1-4) Gal β) seems to be the binding site of the IgM antibody. Interestingly, serum IgG from the patient of Maddison reacted with GD1b, GT1b, and GQ1b, although whether his IgG had antibody activity against GD2 and GD3 was not shown. An absorption study would clarify whether his IgG reacted with a disialosyl residue linked to the internal galactose common to b series gangliosides. An immunohistochemical study showed localisation of GD1b in the neurons of the human dorsal ganglion. GD1b is also localised in the large neurons of the rabbit dorsal root ganglion, and Kusunoki *et al*⁵ succeeded in the development of sensory ataxic neuropathy by sensitisation with GD1b. Autoantibody to b series gangliosides including GD1b may function in the development of acute sensory ataxic neuropathy in some patients.

Anti-GQ1b IgG antibody from patients with Miller Fisher syndrome cross reacts with GT1a. GT1a has a disialosyl residue linked to the external galactose common to GQ1b, and this may be the binding site of the autoantibody. We investigated the fine specificity of anti-GQ1b IgG antibody in serum samples from 82 patients: 56 with Miller Fisher syndrome, 11 with Guillain-Barré syndrome, 13 with Bickerstaff's brain stem encephalitis, and two with acute ophthalmoparesis. External ophthalmoplegia was present in all of these patients. Anti-GQ1b IgG antibodies were absorbed by GT1a in 80 (98%) of the 82 serum samples, by GD1b in 11 (13%), and by the other b series gangliosides GD3, GD2, or GT1b in 24 (29%). The most frequent pattern of fine specificity was the cross reaction with GT1a alone, seen in 56 (68%) samples. By contrast, we recently noted that some patients with the "ataxic form of Guillain-Barré syndrome" showed no or minimal external ophthalmoplegia but had anti-GQ1b IgG antibody. Anti-GQ1b IgG antibody from the patients, as well as those with Miller Fisher syndrome, were absorbed by GT1a. The finding that ataxic Guillain-Barré syndrome and Miller Fisher syndrome have in common an autoantibody with the same fine specificity suggests that they form a continuous range. We should not have used

the term "anti-GQ1b IgG antibody syndrome", but rather, "anti-GQ1b/GT1a IgG antibody syndrome", which includes Miller Fisher syndrome, Guillain-Barré syndrome with ophthalmoplegia, Bickerstaff's brain stem encephalitis, acute ophthalmoparesis without ataxia, and the ataxic form of Guillain-Barré syndrome. Maddison did not show that his patient's IgG had antibody activity against GT1a, but his case could be categorised as the syndrome of acute sensory neuropathy if the patient's IgG did not react with GT1a.

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BOOK REVIEWS

Critical appraisal of medical literature.

By DAVID MARCHEVSKY (Pp 304, £55.25). Published by Kluwer Academic/Plenum Publishers, New York, 2000. ISBN 0-306-46474-8.

This book is written in three parts for medical professionals requiring an introduction to critical appraisal of medical information. The first examines the "justification and validity of medical information", providing "definitions and relevant topics of statistics and epidemiology". The second is devoted to "complementary aspects of systematic critical appraisal of medical information". The third part "presents some statistical techniques that are commonly used in published articles".

It would have been helpful if the reader had been provided with references for the topics discussed and those not pursued. The list of books and published papers given near the end of the book are never referred to in the text. Whereas the Normal and binomial distributions are discussed, no other distributions are covered, in particular the Poisson distribution.

Some readers may find the first few chapters heavy going, but they are worth persevering with. The author should have said that the use of the correlation coefficient for indicating agreement between one test and a gold standard is misleading (see Bland JM

and Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1986, 307-10). In the discussion on confidence intervals, the author should have used the phrase "likely to lie" rather than "assumed to lie". It should have been stated that the relative risk is not appropriate for case-control studies. The terms "multivariable" and "multivariate" are used incorrectly at various places in the text. It should have been made clear that a correlation of zero does not necessarily imply independence.

There are some typographical errors. In particular, in chapter 25, it is the independent variables that are categorical.

The book is clearly written and the subject matter logically developed. It is well suited to its target audience and would be a useful addition to any clinician's bookshelf.

NEVILLE VERLANDER

MRI and CT of the brain. Edited by JAMES E GILLESPIE and ALAN JACKSON (Pp 299, £75.00). Published by Arnold, London, 2000. ISBN 0 340 761 210.

Several large scale textbooks cover much the same ground as this fairly modest, 300 page volume. It is questionable whether the information it contains would be adequate for someone practising or training as a specialist neuroradiologist and, indeed, the preface indicates that it is aimed at general radiologists and those in training, rather than subspecialists. It might be suitable for neuroscience trainees. However, given that, the readers' needs differ substantially from those of the subspecialist, who will already have a grounding in the subject. What does it offer the generalist who has to report on CT and MRI studies?

Part 1 contains two 20 page atlases, one of normal anatomy as displayed by MRI and CT, and another of brain (actually intracranial) pathology. The former contains a sufficient number of typos: "mamillary body", "thalamus" (both repeated), "tuberculum sella", "gyrus recti" to confuse the unwary, plus terms recognised in "radiologists' anatomy" but not found in anatomists' texts, such as "tectal" and "suprasellar" cisterns. This is probably *not* what generalists hoping to hone their neuroradiological skills need. What they do require, but will not find here, are extensive examples of confusing normal variants, artefactual abnormalities, and things which resemble others the management of which is radically different. In this respect, the implied message on page 38, for example, that extensive parenchymal calcification on CT usually indicates metabolic disease (and should presumably prompt further investigation) is not overly helpful.

In Part 2, eight chapters, each with about 20 pages and 30 illustrations, deal with the usual topics: trauma, congenital abnormalities, infections and inflammatory diseases, etc, and two shorter ones cover hydrocephalus and "advanced techniques in neuroradiology". The last has, I think, no part in such a book: most of what it deals with, although generating grants and increasing congress expenses in academic departments, has nothing to do with clinical neuroradiology in the DGH—or anywhere else. Conversely, a more exhaustive treatment of hydrocephalus would have been justified, given the frequency with

which it raises its ugly head in reports by non-specialist radiologists, and the confusion created by most texts on its imaging and diagnosis. Possibly the authors, too, found it a difficult topic; they certainly repeat the chestnut that flow void in the third ventricle on T2 weighted images indicates communicating hydrocephalus, the error of which is demonstrated anew by figs 1.29 (lissencephaly), 1.26 (agenesis of the corpus callosum), and 6.26 (lacunes).

It is difficult to know how much room to give rare conditions; several things a generalist is unlikely to encounter are both described and illustrated, whereas some more common lesions receive less detailed attention. Only one chapter gives a list of protocols for investigation based on clinical presentation which, although one might quarrel with minor details, does seem what the generalist needs. Another (on trauma) essentially deals with a single presentation, and rightly emphasises the value of CT; given its target audience, it could be argued that the text as a whole might more sensibly have been arranged along such lines (acute headache, epilepsy, dementia) and/or by radiological appearances (calcified masses, small periventricular high signal foci on T2 weighted images, multiple ring enhancing lesions), with at least one specific chapter on children, rather than assuming that the reader already has a good idea whether he or she is looking for or at a neoplastic, inflammatory, or congenital lesion. Unfashionable (and, for the DGH radiologist, economically unpopular) though it may be to say so, many queues in which patients camp for months outside their MRI units would disappear overnight were the experts to come clean and confess that that most things which really matter can be shown by CT of modest quality!

The editors work in Manchester, which may explain their claim in the preface that CT dates from 1973 (when it arrived there, more than a year after Ambrose started work at Atkinson Morley's). Most of the contributors (12 neuroradiologists and one scientist—a physicist, I presume) are relatively young. Their literary talents vary, but the chapters are in general well prepared and the standard of the illustrations is high; frank errors are relatively rare. Given the British provenance of the book I was, as usual, distressed by the arguably excessive reliance of almost all the contributors on the transatlantic literature. Some chapters are heavily, others sparsely referenced; the index is reasonably full.

IVAN MOSELEY

CORRECTION

ED Ross, DM Orbelo, J Cartwright, et al. Affective-prosodic deficits in schizophrenia: profiles of patients with brain damage and comparison with relation to schizophrenic symptoms. *J Neurol Neurosurg Psychiatry* 2001;70:597-604. During the editing process, the title was misquoted. It should read "Affective-prosodic deficits in schizophrenia: comparison to patients with brain damage and relation to schizophrenic symptoms."

The author's email address should also be changed to read elliott-ross@ouhsc.edu